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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,078	11/08/2001	Donna T. Ward	RTS-0236	6940

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,078	WARD ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2003 and 09 January 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15,20-24 and 26-40* is/are pending in the application.

4a) Of the above claim(s) *32-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-15, 20-24, and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed November 10, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed March 12, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. Reciept of applicant's letter entered January 9, 2004, indicating that an amendment submitted August 21, 2003 was received too late by the Office for consideration of the Office action mailed August 25, 2003 is acknowledged. To clarify the record, applicants have agreed that the amendment submitted August 21, 2003 is superseded by the amendment submitted November 25, 2003, and that the August amendment will go unexamined. Accordingly, the amendment of claims submitted November 25, 2003 is considered herein.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

4. Newly submitted claims 32-40 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the instant application was subject to a restriction requirement mailed November 1, 2002, which directed applicant to choose one sequence for prosecution. The newly introduced claims are not readable on the elected invention because the multiple regions or oligos now claimed by applicant are distinct and impose a search burden on the Office to search the entire scope of the claimed invention. In

the response to the restriction requirement dated December 2, 2002, applicant canceled a claim that introduced multiple target regions in order to comply with the restriction response. Said response was considered responsive because the remaining claims read only on the broad target of SEQ ID NO: 3. However, applicants' instant amendment, directed to multiple and specific regions of SEQ ID NO: 3 referred to either by region or by nucleobase, and multiple oligos targeting such regions, effectively claims multiple and distinct targets or oligos, each requiring a different search, because a search for one region or oligos does not reveal art against another, and furthermore, a search for art against the whole target of the originally claimed target of SEQ ID NO: 3 does not result in a complete and exhaustive list of all art directed against all of applicants newly defined regions. Therefore, because the newly amended claims are directed to multiple distinct target regions or oligos, this response is considered to introduce multiple new inventions. The requirement is still deemed proper and is therefore made FINAL.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 32-40 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

5. Claims 15, 20-24, 26-28, and 30 are rejected under 35 U.S.C. 112, 1st paragraph, because the specification, while being enabling for antisense-mediated inhibition of EIF2C1 expression *in vitro*, does not reasonably provide enablement for antisense-mediated modulation of an endogenous RNA-mediated interference pathway *in vivo*. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claims 15, 28, and 30 are included in this rejection of record insofar as they are also drawn to methods of using the instantly claimed compounds *in vivo*. This rejection is repeated for the same reasons of record as set forth in the Office action mailed May 7, 2002, but is newly applied against amended claims 21-24. Said claims have been amended such that they now are subject to the instant rejection of record.

Applicant dispute the rejection of record by asserting that "Agami et al. would not lead one of skill in the art to believe that RNAi technology or antisense technology is unpredictable." Applicant cites a passage from Agami which purportedly supports applicants' contention that nothing in Agami et al. states that the instantly claimed methods will not work *in vivo*: "

> Using this [RNAi] method it was possible to suppress gene expression to the extent that the gene function is lost and to inhibit the replication of HIV and RNA viruses in human cells. As it stands, the application of *siRNAs* for disease and gene therapies can follow the existing tools that are already applicable for clinical trials of anti-sense strategies to inhibit gene expression. However, a major drawback of this technology is its transient effect. Gene could only be inactivated for a week. "

From this, applicant contend that "the only limitation that the Agami reference discusses is getting persistent inhibition (i.e. more than one week)".

In response, it is noted that contrary to the "only limitation" indicated above, this passage merely reinforces the position for which Agami was relied upon in the previous Office action, that is, that RNAi and antisense are subject to a similar analysis of enablement since they are both nucleic acid inhibitors. This passage demonstrates the relevance of the citations of the previous Office action, which were in turn cited to indicate the non-enablement of both antisense

and RNAi *in vivo*. Furthermore, this passage cites that gene function was lost only in human cells (*in vitro*), which makes it a peculiar passage to cite in support of the *in vivo* enablement of applicants' claims, because the passage does not indicate predictability *in vivo*, and thus enablement, of nucleic acid inhibitors in methods of use *in vivo*. While it does state that the application of siRNAs for disease and gene therapies can follow existing tools that are already applicable for clinical trials of antisense strategies to inhibit gene expression, it does not indicate that such trials are predictable. To the contrary, throughout the 5 review articles cited previously, it is maintained that the *in vivo* use of nucleic acid inhibitors, while of great promise and potential, simply remain unpredictable insofar as their use *in vivo*.

Applicant is of the opinion that the Office is mistaking the efficacy of a compound (defined by applicant as ultimately curing a disease) with whether the claims are patentable. Applicant takes issue with the citation of Crooke in a previous Office action, which states that one cannot predict *in vivo* pharmacokinetics of nucleic acid inhibitors based on *in vitro* studies, and assert that such a statement does not matter, because *in vivo* pharmacokinetic behavior is only relevant in considerations of the FDA. Applicant repeatedly emphasizes their belief that they are being held to an FDA standard of approval throughout their arguments, and state that even if the compounds of the present invention inhibit the expression of EIF2C1 for a fleeting mount of time the method is still embraced by the claims and is enabled.

For the record, nowhere has applicant been told that they are being held to an FDA standard to be considered enabled, not now, nor anywhere in the prosecution history. If applicant believes a clear statement by the Office to that effect has been set forth, applicant is invited to point out with particularity where on the record such a statement might appear. It appears that

contrary to being held to an FDA standard, applicant is using such a charge in a strained invalidation of the Crooke et al. and other references. Applicant is reminded that the standard for enablement rests principally on whether the claimed methods are unpredictable, and whether such unpredictability leads to undue trial and error experimentation. Since applicant has not exemplified any *in vivo* results, applicants' arguments rely principally on the enablement of the prior art. Thus the statement by Crooke et al. that *in vitro* results cannot be applied to the prediction of *in vivo* pharmacokinetics seems particularly relevant, since the applicability of *in vitro* results to forecast *in vivo* success is the basis of the instant enablement rejection. It is furthermore difficult to extrapolate from the Office's citation of this statement to the position that somehow applicant has thus been required to submit phase III FDA data as suggested by their arguments, since no reference to the FDA, humans, controls, doses, toxicities, or clinical trials can be found in the passage.

Applicant cites several more passages to forward their belief that this improper FDA-type level is being enforced; however, applicant can only point to the Office's citation of passages from review articles, not from any text written by the examiner. , whereupon a similar strained comparison is made to FDA standards. For example, applicant cites the Office's reference to Gewirtz et al. that "[w]ithout the ability to [deliver ODN into cells and have them reach their target], it is clear that even an appropriately targeted sequence is not likely to be efficient." Based in this quote from a review article, applicant concludes that the Office is requiring their compounds to be "efficient", and assert that this is not a concern of the Office in considering the patentability of the claims.

In response, it is pointed out that this quote is from a review article cited to support the unpredictability inherent in targeting antisense to the appropriate biological site, and has not been held as a standard that applicant must meet. As stated above, a primary consideration of the patentability of the pending claims is whether the methods under consideration are considered unpredictable, and whether such unpredictability would result in undue experimentation. Applicants' focus on the word "efficient" (provided as a quote from a reference, not generated by the Office) glides over the reality that the passage indicates unpredictability in how well (i.e. how efficiently) antisense nucleic acids reach their targets. Furthermore, applicants' arguments that the Office may not evoke any phrase with the term "efficient" in it is misguided. The American Heritage® Dictionary of the English Language, (Fourth Edition Copyright © 2000 by Houghton Mifflin Company defines "efficient" as the "power or capacity to produce a desired effect; effectiveness." According to applicants' arguments, the Office, in considering the enablement of an invention, would be unable to consider "the power or capacity to produce a desired effect". Moreover, the Office was not providing this passage as an indication that applicants' invention is not efficient, but rather to underscore the unpredictability of appropriate delivery of such molecules, which was raised in the outstanding enablement rejection as a major consideration of unpredictability. The passage of Gewirtz supports this point.

Applicant had previously submitted several papers that were considered by the examiner in support of their claim of enablement. Applicant disagrees with the examiners' response thereto, which said *inter alia* that the results from these single experiments, performed in organisms not found in nature do not outweigh the multitudes of art cited in the 5 review articles. Applicant asserts that although some of the mice may have been generated to be immuno-

compromised, there are numerous organisms in "nature" that are also immuno-compromised (e.g. individuals with HIV, cancer, and the like). Applicant concludes that whether or not these organisms are found in nature is not relevant to the pending claims, and whether or not these experiments would be satisfactory for the compounds to be approved by the FDA is unknown.

It is reiterated that applicant is not currently being, nor ever have been held to an FDA standard. It is maintained that the experiments cited by applicant, which utilize Severe Immune Combined Deficient (SCID) mice, are not representative of the breadth of applicants' claims, which are encompass *in vivo* methods of use in any animal. Applicant is reminded that the scope of results using different compounds directed to different targets reported in SCID mice does not match the instantly claimed scope embracing any animal.

Response to Claim Rejections - 35 USC § 102/103

6. Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Koesters et al. (of record) and claims 1, 2, 12 and 14 are also rejected under 35 U.S.C. 102(e) and 103(a) as being anticipated and/or obvious by Schalling et al. (U.S. Patent Number 5,695,933), for the same reasons of record as set forth in the Office actin mailed August 25, 2003.

Applicant has amended claim 1 to recite the limitation that the claimed compounds must inhibit the expression of EIF2C1 by at least 42%. It was set forth in the previous Office action that although the references of Koesters et al. and Schalling et al. do not specifically teach the function of inhibiting applicants' instant SEQ ID NO: 3 as claimed in the present application, the

compounds of Koesters et al. and Schalling et al. meet all the structural limitations as set forth in the instant claims. Because the sequences are substantially identical to applicant's claimed compounds, in the absence of evidence to the contrary said compounds are thus considered to possess the functional limitations of specifically hybridizing with and inhibiting the expression of applicants' instant SEQ ID NO: **3**. Support for this conclusion is drawn from MPEP 2112:

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection**. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

Applicant points out that since M.P.E.P. § 2112.01 indicates that a *prima facie* of case can be rebutted by evidence showing that thc prior art products do not necessarily possess the characteristics of the claimed product, and because table 1 of the instant application indicates that some oligos contained therein did not inhibit to the level of 42% as now claimed, that sufficient evidence has been presented to overcome the *prima facie* case.

This position is not adopted. Table 1 indeed describes some oligos that do not inhibit to the level of 42% as now claimed, but most of the oligos listed in said table exceed the 42% threshold. M.P.E.P. § 2112.01 sets forth the following:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Since the Office has shown a sound basis for believing that the products of the applicant and the prior art are the same, applicant has the burden of showing they are not. Merely pointing to a table that shows that most of the disclosed oligos exceed the claimed degree of bioactivity does not indicate in any way whether the *oligos of the prior art* possess such bioactivity. Thus, table 1 is not considered to show that the oligos of the prior art do not necessarily possess the claimed activity.

Claim Rejections - 35 USC § 103

7. Claims 1, 2, 4-15, 20, 24 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koesters et al., in view of Cikaluk et al. (Mol. Biol. Cell, 1999. v10:3357-3372), Taylor et al., Baracchini et al., and Milner et al.

Applicant traverses the instant rejection on the grounds that the Office failed to establish a *prima facie* case of obviousness, because the Office failed to provide any motivation to modify the cited references to make the instant invention obvious.

In response to the allegation that there is no motivation to inhibit applicants instant target, applicant is reminded that Koesters et al. teach applicants' instantly claimed sequence, and importantly, teach on page 217 (last paragraph) the instant target of EIF2C1 is overexpressed in Wilms tumors, which makes "human EIF2C1 an interesting candidate for potential involvement in Wilms tumorigenesis". Furthermore, Cikaluk et al. expressly teach antisense RNA-mediated inhibition of GERp95, the C. elegans orthologue of applicants instant EIF2C1 target of SEQ ID NO: 3. Finally, Taylor et al. teach the use of antisense oligos to inhibit any gene of known sequence as a research tool for the elucidation of gene function. Since Koesters teach that

applicants target of SEQ ID NO: 3 is an interesting candidate for involvement in Wilms tumorigenesis, and because Cikuluk already used RNA antisense compounds to inhibit a homologous transcript in another species, and finally because Taylor et al. teach that antisense can be used to inhibit any gene of known sequence, one of skill would have been motivated to inhibit applicants instant target to investigate its role in tumorigenesis and development.

The remainder of applicants' arguments argue each reference individually and point out that each reference does not teach some element of applicants' claims. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is acknowledged that the references when viewed individually do not teach the presently claimed invention; however, the test for obviousness is what the *combined* teaching of the prior art would have suggested to those of ordinary skill in the art.

For example, applicant argues that Cikaluk reports RNAi inhibition of GERp95, but that Cikaluk "fails to teach or even suggest a nucleotide sequence that is identical to SEQ ID NO: 3 of the present application." Applicant is reminded that Cikaluk was not relied upon for the teaching of SEQ ID NO: 3, but rather the c. elegans homolog of SEQ ID NO: 3. The teaching of SEQ ID NO: 3 comes from Koesters et al., who also describe its potential role in tumorigenesis. Applicants do not argue that GERp95 is not related to the instant SEQ ID NO: 3. Finally applicants state that Cikaluk fails to teach all the elements of the claimed invention. Again, applicant is reminded that this is not a rejection under 35 U.S.C. § 102. Cikaluk teaches RNA-mediated inhibition of the c. elegans homolog, and was relied upon for this alone. Most of

applicants' remaining arguments proceed along a similar line, where each reference is indicted for its failure to teach an element for which it was not relied upon in the instant rejection, and for failure to teach each and every element of applicants' claimed invention. Such arguments are responded to as above, and are not considered convincing.

Applicants also argue that at best there "an obvious to try" standard has been employed, and that the combination of references does not provide one of skill in the art an "expectation of success." Applicants argue that there is nothing within the references, either alone or in combination, that would lead one of skill in the art to expect that antisense molecules would inhibit the expression of EIF2C1 by at least 42%, and that Table 1 provides examples of compounds did not inhibit the expression of EIF2C1 by at least 42%. Applicants assert that until the present invention there was no evidence that inhibition of EIF2C1 by at least 42% would occur, and that therefore the claimed invention is not obvious.

This argument is not considered convincing, because Taylor et al. teach that with modern software screening programs and high-affinity chimeras, one of ordinary skill in the art would have to screen only 3-6 oligos in order to generate one that inhibits 66-95%. Furthermore, Milner et al. teach methods for high throughput screening of oligonucleotides that would be expected to achieve the requisite level of inhibition. Significantly, Milner indicates that such screening can be done in a controlled manner with the expectation that oligos will be found that inhibit to a significant degree. Finally, Baracchini et al. teach compounds and methods of making antisense molecules that describe in detail procedures relating to synthesis of antisense oligos, including starting reagents and supplier names, equipment manufacturers, incubation times, cell lines, concentrations, and assays for determining the level of inhibition achieved, *all of which are*

identical to those taught in applicants' specification, published 3 years prior to applicants' earliest priority date. Clearly, the claim that the instant invention is merely "obvious to try" is not applicable here. For these reasons the invention as claimed by applicants are considered *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James Douglas Schultz, PhD

SEAN McGARRY
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1635